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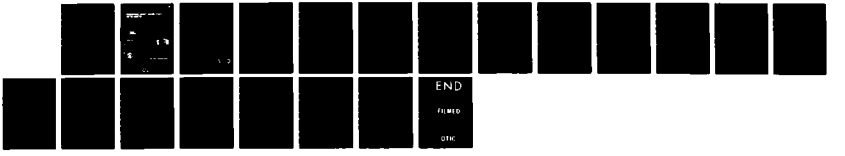

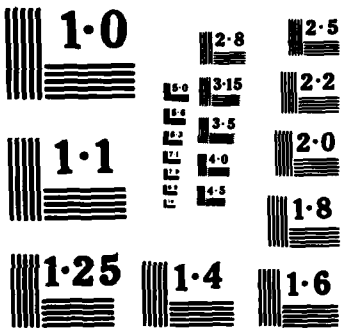

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Benzodiazepine Activity: Daytime Effects and the Sleep EEG[1]

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To expedite communication of our research findings, this report is being circulated as a preprint and, if cited, should be listed as a personal communication. The paper will appear in Clinical Neuropharmacology.

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SUMMARY

Recently, research emphasis has shifted from assessment of efficacy of benzodiazepine hypnotics to investigation of pharmacokinetics and pharmacodynamics. In this paper, we review our work and draw upon the published literature to examine the effects of benzodiazepine hypnotics on the structure of sleep, arousal threshold during sleep, and the impact of bedtime hypnotic use on next-day performance. We also describe the effects of discontinuation of use of long and short half-life sedative-hypnotics.

The most characteristics changes in sleep structure associated with benzodiazepine use are the decrease in Stage 4 sleep and the resultant increase in Stage 2 sleep. Correspondingly, an analysis of the EEG shows a decrease in delta wave count and an increase in sleep spindle rate. The decrease in delta waves occurs gradually over 3-4 days of use, while the spindle rate increase occurs immediately. These EEG changes were first noted following use of flurazepam. Flurazepam has a long half-life metabolite, N-desalkylflurazepam, which accumulates in plasma over consecutive nights of use. Our more recent studies of triazolam, a short half-life benzodiazepine, have demonstrated that the pattern of EEG change during treatment is similar for the two drugs, as is the gradual return to baseline during withdrawal.

Similarly, both flurazepam and triazolam produce the same kinds and time course of effects on arousal threshold during sleep.

In the assessment of next-day performance, with chronic use, dose level, rather than half-life, is the best predictor of adverse effects on tasks sensitive to benzodiazepines. No sedative-hypnotic has been found to improve next-day performance above placebo values. In single and acute dose administration and at comparable dose levels, shorter half-life hypnotics are less likely to produce daytime impairment.

It has been reported that withdrawal from short half-life hypnotics produces poorer sleep, termed "rebound insomnia". This withdrawal effect has not been described for long half-life benzodiazepines. However, our work indicates that poor sleep may occur in some patients withdrawing from flurazepam but the poor sleep, if it occurs, tends to occur after withdrawal night 4, sometime within a two-week period. The cause of this poor sleep is uncertain as it is not related to residual N-desalkylflurazepam plasma levels in patients who had received flurazepam. For benzodiazepines with a short half-life, poor sleep, if present, occurs early during the withdrawal period, most often on withdrawal nights 1 or 2.

Our results indicate that the half-life of benzodiazepine hypnotics is not the best predictor of next-day performance effects, arousal threshold effects, or the nature of EEG changes during sleep. Other pharmacokinetic properties, such as volume of distribution, must also be considered. Long and short half-life benzodiazepines both may produce a "rebound insomnia", although the time of occurrence seems to

differ. The marked individual differences in response to similar drug plasma levels plus processes of tolerance and adaptation limit the probability that significant correlations between plasma levels and behavioral levels will be found over individuals during chronic use. Dose level is the best predictor of next-day effects and, so, the smallest effective dose should be prescribed.

INTRODUCTION

Though the use of sedative-hypnotics has decreased in the past decade, they are still widely prescribed. In the latest national survey of the use of psychotherapeutic drugs in the United States, Mellinger and Balter (1981) reported that hypnotics followed antianxiety drugs in prevalence of use. Mellinger and Balter (1981) reported that women [3.02%] more frequently use sedative-hypnotics than men [2.1%] and, as expected, the use increases with age. Most sleep experts now believe that short-term use of sedative-hypnotics is most appropriate for transient or acute episodes of insomnia, and the survey findings reflect this attitude. Short-term or infrequent use was more common than long-term daily use. Of those using hypnotics in the preceding year of the study, 61 percent used them for seven nights or less. But ten percent used them nightly for the year, contrary to both pharmaceutical recommendations and best medical advice and well beyond the measured period of efficacy. The survey found that the benzodiazepines were the most frequently prescribed hypnotics. This paper will only be concerned with the benzodiazepine hypnotics.

The pharmaceutical companies must, of course, demonstrate efficacy to attain Federal Drug Administration (FDA) approval, but research emphasis is shifting from efficacy to pharmacokinetics and pharmacodynamics of the benzodiazepines. Controlled studies have shown that all the benzodiazepine hypnotics are effective in inducing and maintaining sleep for some period of time. In this paper, we will review our work and draw upon the published literature to look at the effects of benzodiazepine hypnotics on the structure of sleep, with particular attention to the EEG changes, arousal threshold during sleep, and the impact of the hypnotic on next-day performance, and, finally, we will look at the impact on sleep when the hypnotic is discontinued. We will examine the importance of dose level and half-life in each of these areas.

Most of our data have been obtained from studies using flurazepam, whose active metabolite N-desalkylflurazepam has a reported half-life of 24-100 hours, and triazolam, whose half-life is 2-3 hours. The contrast in plasma level with chronic use of these two drugs is illustrated in Figure 1 (Johnson et al. 1983).

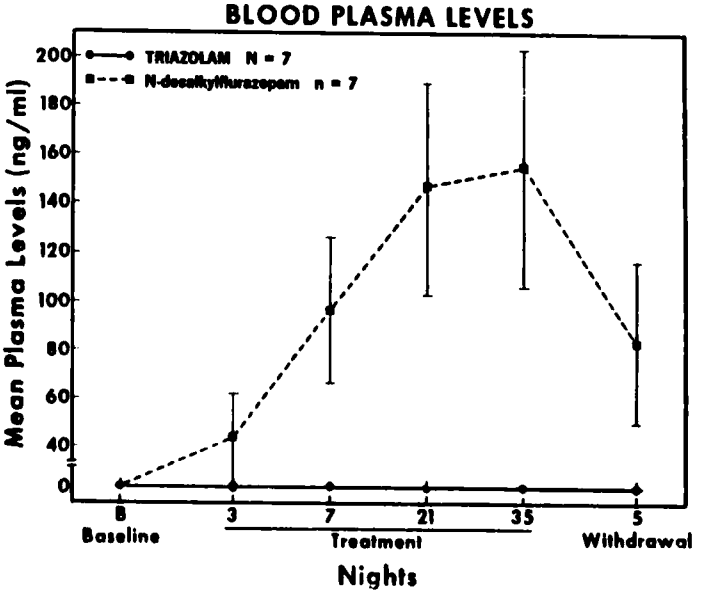

Fig. 1. Blood plasma levels of triazolam and N-desalkylflurazepam during baseline, treatment, and withdrawal (from Johnson et al. 1983).

The expected build-up of N-desalkylflurazepam was clearly present, but there was no detectable accumulation of triazolam in plasma.

Effects During Sleep

The most characteristic changes in the sleep structure with benzodiazepine use are the decrease in Stage 4 and the resultant increase in Stage 2. The effect on REM sleep amount varies from study to study. REM latency may be increased, thus reducing REM percent, especially in the first hours of sleep (Gaillard et al. 1973).

EEG Changes: In addition to sleep stage scoring, we have obtained quantitative measures of the change in delta activity, as well as change in sleep spindle rate during sleep. As shown in Figure 2, the decrease in delta activity is a gradual change over the first three to four days of use. Our research has shown that both amplitude and the number of delta waves in nonREM (NREM) sleep are reduced with benzodiazepine hypnotic use (Johnson et al. 1979).

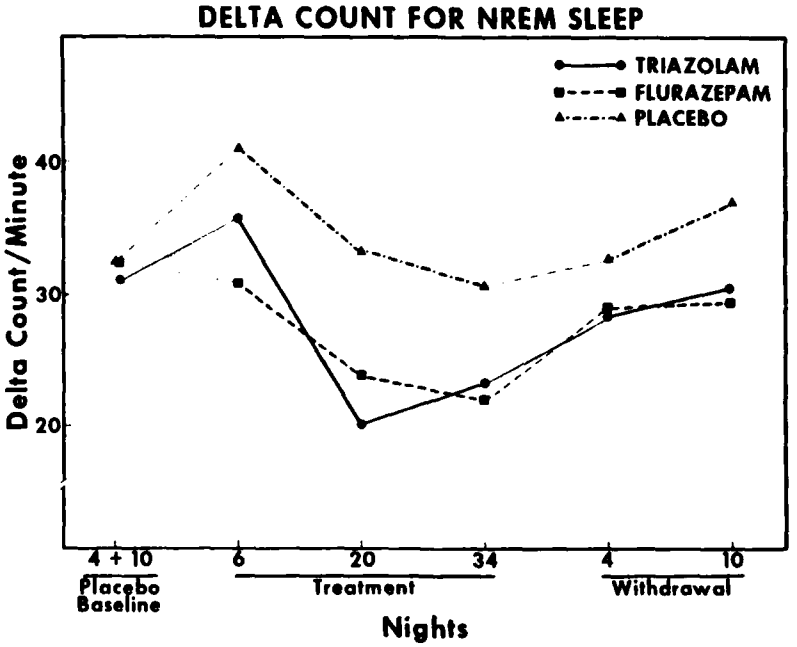

Fig. 2. Delta count per minute in patients receiving either triazolam (0.5 mg), flurazepam (30 mg), or a placebo during baseline treatment and with drawal (from Johnson et al. 1983).

Spindle rate per minute increases more quickly with benzodiazepine hypnotic use, in contrast to the more gradual reduction in delta. This increase occurs for many benzodiazepines on the first night of use. The increase in sleep spindles occurs in

all stages of NREM sleep, but is most clearly seen in Stage 2. There is no time of night effect for these hypnotic-induced increases in spindle activity. Spindle rate changes are illustrated in Figure 3.

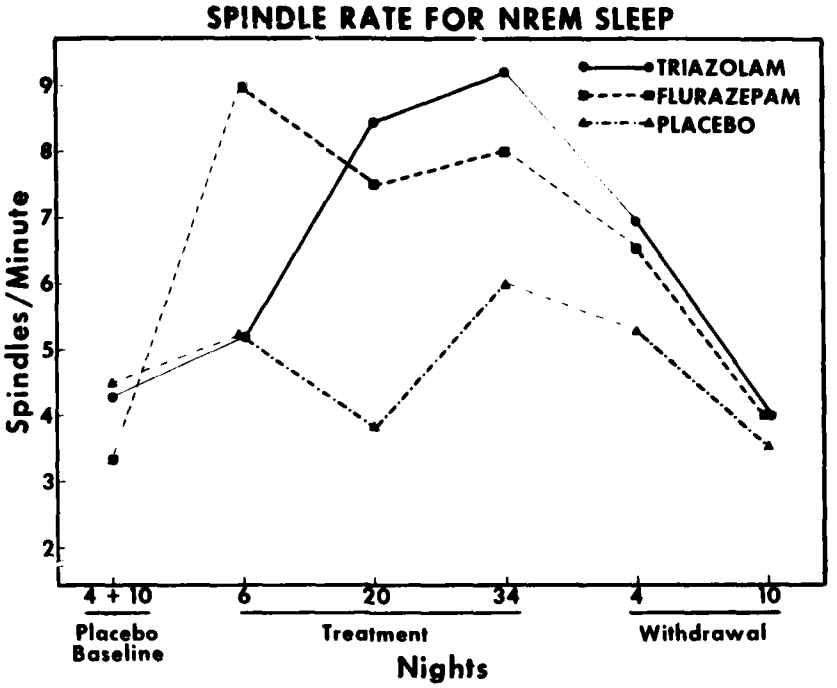

Fig. 3. Sleep spindle rate per minute in patients receiving either triazolam (0.5 mg), flurazepam (30 mg), or placebo during baseline treatment and withdrawal (from Johnson et al. 1983).

These EEG changes were first noted following use of a long half-life benzodiazepine in which there was a build-up of an active metabolite with chronic use, e.g., flurazepam. It was generally assumed that the build-up of the metabolite N-desalkylflurazepam was causally related to the EEG changes with intermediate or chronic use.

In 1981, we examined the EEG changes produced by a short half-life benzodiazepine, triazolam (0.5 mg), and found the same decrease in delta and increase in sleep spindles over a six-night period (Johnson and Spinweber 1981). A collaborative effort with Dr. William C. Dement and his staff at Stanford University provided us the opportunity to examine the EEG changes produced by flurazepam (30 mg) and triazolam (0.5 mg) over 37 nights of use. This study also included a two-week withdrawal period (Johnson et al. 1983).

Not only did we find that the pattern of EEG change during treatment was similar for these two drugs, but so was the gradual return to baseline during withdrawal. Also,

of interest were the findings that these EEG changes, though plateauing after three weeks of drug use, never showed any signs of tolerance. This failure to show a return to or drift toward baseline with chronic use is in contrast to the adaptation seen in measures of daytime performance and in efficacy.

It is clear from these data that these EEG changes are not related to the half-lives of these two compounds. For those patients receiving flurazepam, correlations were computed between plasma levels of N-desalkylflurazepam and both the amount of delta and spindle activity and the changes in these two EEG measures from baseline. The correlations were not significant in any time period of the study for either amount or change in delta or spindle activity (Johnson et al. 1983).

In a just completed study, we examined the effect of dose level on delta and sleep spindle EEG changes. In this study, thirty-six subjects, 12 in each group, were given either 0.25 or 0.5 mg triazolam or a placebo for five nights. Sleep was recorded every night, and on the third night, EEG delta waves and sleep spindles were counted on line using a delta and spindle detector (Johnson and Spinweber 1981). The overall average total delta count was 9.5, 4.6 and 2.7 per minute for the placebo, low, and high triazolam groups respectively. The group differences were significant, $P<.004$. As might be expected, SWS percent for the three groups averaged over all five nights of sleep followed the findings for the delta count, 19, 13, and 9 percent for placebo, 0.25 mg, and 0.5 mg groups respectively. The spindle rate per minute was lowest for the placebo group and highest for those receiving 0.5 mg triazolam with the 0.25 group in between. The difference between the three groups was significant at the 0.035 level, one-tailed test.

Our recently acquired results are supported by studies that have examined changes in sleep structure and sleep stages at differing dose levels. Gaillard et al. (1973) examined sleep stage changes at two dose levels of three benzodiazepines: nitrazepam (10 mg and 30 mg), flunitrazepam (2 mg and 6 mg), and bromazepam (9 mg and 27 mg). These dose levels were selected as being clinically comparable. The pattern of sleep stage and sleep structure changes was similar for all three hypnotics and, in all instances, the changes were directly related to dose level. For example, in the nitrazepam patients, baseline slow wave sleep (SWS) percent was 18.6. On 10 mg nitrazepam, SWS percent was reduced to 12.0 and to 4.9 when 30 mg were given. The respective REM latencies were 108, 137, and 260 minutes. The differences in half-lives for the three hypnotics did not appear to be a factor in the results and were not discussed by Gaillard et al. We should emphasize at this time that these EEG changes are not related to perceived quality of sleep nor are they significantly related to daytime performance or mood. These EEG changes, however, do appear to be a more sensitive electrophysiological indicator of the central nervous system (CNS) presence of benzodiazepines than is blood plasma level.

Arousal Level: SWS is generally referred to as "deep sleep" and it would be reasonable to assume that, since there is a decrease in SWS with benzodiazepine use, arousal threshold would decrease. Sleep should be lighter. Both subjective and

objective data indicate that quite the reverse is true. Compared to a placebo, both flurazepam and triazolam significantly increase arousal threshold, especially during the first two hours of sleep. For example, the arousal threshold to a brief 2-second 1,000 Hz tone during the second hour of sleep increased to a level near 110 dB. After placebo ingestion, the threshold for this time period was nearer 80 dB.

As with the EEG changes, we found a similar pattern of increase and decrease in arousal threshold when we examined the effects of flurazepam (30 mg) and triazolam (0.5 mg) (Johnson and Spinweber 1983).

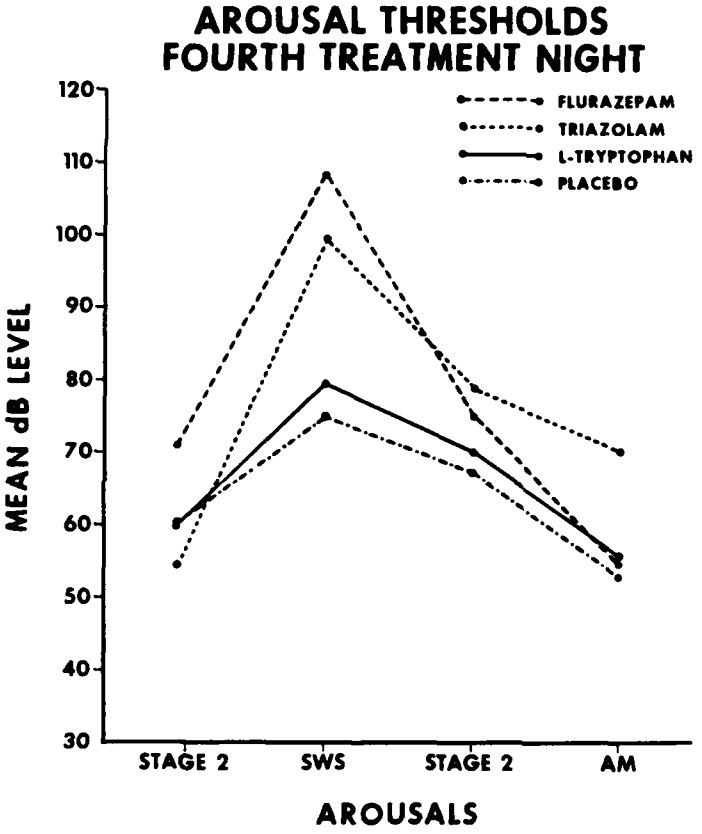

Fig. 4. Comparison of mean arousal thresholds for separate laboratory studies of flurazepam (30 mg), triazolam (0.5 mg), and l-tryptophan (3 g). The placebo values represent combined placebo data from the three studies.

Data in Figure 4 are from the fourth night of use for both hypnotics and these data clearly illustrate that the time of the peak arousal threshold and the time course of the gradual return to presleep levels were similar. In an unpublished study, we have aided sleep onset by giving 3 grams of l-tryptophan to a similar sample of young adult (mean age 21.0 years) subjects. After three nights of ingestion, l-tryptophan significantly reduced sleep latency, but note in Figure 4 that l-tryptophan did not increase arousal threshold. The arousal threshold was similar to that of subjects receiving a placebo. This comparison highlights the sedative qualities of the benzodiazepines in contrast to the "natural" sleep-inducing qualities of l-tryptophan.

In summary, during sleep, changes in EEG activity and arousal threshold appear to be similar for both long half-life and short half-life benzodiazepine hypnotics. We anticipate that, as more studies with varying dose levels are reported, dose level will be a more important factor than half-life with respect to changes in the electrophysiology of sleep and in arousal thresholds.

Daytime Performance

Task Sensitivity: Examination of next-day performance effects clearly shows that dose level, and not half-life, was the best predictor of performance decrement. There have been no reports of significant performance enhancement following sedative-hypnotic use when next-day performance was compared to that seen after placebo ingestion (Johnson and Chernik 1982). At the higher dose levels, use of all sedative-hypnotics led to next-day performance decrement on one or more tasks.

In their review paper, Johnson and Chernik (1982) examined 52 studies in which performance data were obtained the next day following bedtime ingestion of a sedative-hypnotic or a placebo. Most of these studies used noninsomniac young adult males and the laboratory tasks involved psychomotor skills. Drug-related improvement was not found. But, as mentioned in the review paper, there are no convincing data that chronic insomniacs' daytime performance is significantly impaired. Thus, it may not be reasonable to expect performance to improve following hypnotic use. Further, for most insomniacs, the EEG-recorded sleep quantity is better than that subjectively reported (Carskadon et al. 1976) and the increase in total sleep time with a sedative-hypnotic averages less than 30 minutes (Solomon 1979). Transient insomniacs should benefit most from hypnotic use, but the nature of the problem precludes the easy obtaining of baseline data for the evaluation of drug effects in transient insomniacs.

When the type of performance impairment produced was considered as a factor, it was clear that certain tasks were more likely to show a drug effect than others. Speed of performance was found to be most drug-sensitive. Three of the five most drug-sensitive tasks listed in Table 1 involve speed plus a cognitive component, i.e., card sorting, symbol copying, and the digit symbol substitution test. All the tasks also have a motor component. Choice reaction time shows a greater drug effect than does simple reaction time. The least drug-sensitive tasks, listed in Table 1, coordination (balance board), critical flicker fusion, and rotary pursuit, are not timed tests. Purdue pegboard is timed, but has no cognitive component.

A consistent finding when memory was measured was that of anterograde amnesia following benzodiazepine use (Bixler et al. 1979, Roth et al. 1980, Spinweber and Johnson 1982). Information presented during the night following bedtime ingestion of a benzodiazepine sedative-hypnotic was significantly less likely to be recalled the next morning when compared to subjects receiving a placebo. Information learned prior to drug ingestion was not affected (Spinweber and Johnson 1982). It is unclear at this time what mechanisms cause this amnesic effect, but the more rapid

return to sleep of patients taking the sedative-hypnotic may reduce consolidation time (Roehrs et al. 1983). In the recently completed study mentioned earlier, we kept our 36 subjects awake for 15 minutes after having been given a list of words. Subjects who had received 0.25 mg or 0.5 mg dose of triazolam at bedtime recalled fewer words the next morning than did subjects who had received the placebo. Memory was most impaired in those subjects who had received the 0.5 mg dose. Clinical reports of amnesia for next-day events following ingestion of a short half-life benzodiazepine the night before indicates that memory impairment occurs in the

Table 1

Benzodiazepine effects on performance in normal subjects[1]

Test	Number of benzodiazepines tested	Number of test comparisons	Decrements[2]	
			Number	Percent
Card sorting	5	18	11	61
Symbol copying	3	8	4	50
Tapping rate	3	13	6	46
Digit symbol substitution test	6	31	13	42
Memory	6	17	6	35
Arithmetic	6	20	7	35
Vigilance	3	9	3	33
Tracking task	8	17	5	29
Cancellation task	3	11	3	27
Choice reaction time	7	44	10	23
Simple reaction time	4	22	5	23
Purdue pegboard/ manual dexterity	4	11	2	18
Rotary pursuit	3	6	1	17
Critical flicker fusion	6	31	2	6
Coordination	4	12	0	0
Total		270	78	29

[1] From Johnson and Chernik (1982)
[2] Statistical comparisons showing drug-related impairment compared to performance on placebo

absence of sleep and the effect persists some 14 to 20 hours post ingestion (Shader and Greenblatt 1983). The early return to sleep, thus, does not appear to fully explain the anterograde amnesia.

Dose Level: As noted above, at the higher dose levels (Table 2), use of all benzodiazepines was associated with impairment of daytime performance. In contrast,

Table 2

Benzodiazepine dose level and performance in normal subjects[1]

Benzodiazepine	Dose (mg)	Number of test comparisons	Decrements[2]	
			Number	Percent
Clobazam	10	2	0	0
	20	14	3	21
	30	7	0	0
	40	4	0	0
Diazepam	5	2	0	0
	10	2	0	0
	15	1	1	100
Flunitrazepam	0.25	1	0	0
	0.5	1	0	0
	1	11	4	36
	2	8	4	50
Flurazepam	15	25	2	8
	30	38	17	45
Nitrazepam	2.5	7	0	0
	5	38	8	21
	10	35	24	69
Oxazepam	15	1	0	0
	30	1	0	0
	45	1	1	100
Temazepam	10	4	0	0
	15	9	0	0
	20	4	0	0
	30	16	2	13
	40	6	3	50
	60	6	2	33
Triazolam	0.25	6	0	0
	0.5	15	5	33
	1	2	2	100
Total		267	78	24

[1] From Johnson and Chernik (1982)
[2] Statistical comparisons showing drug-related impairment compared to performance on placebo

at the lower dose levels, there were few significant differences in daytime performance when the placebo and drug subjects were compared. For example, as summarized in Table 2, when patients taking flurazepam (15 mg) and those receiving a placebo were compared on the performance of 25 tasks, the performance of the flurazepam patients was significantly impaired in only two of the tasks (8%). In contrast, when the performance of patients taking flurazepam (30 mg) was compared to placebo patients, 17 of the 38 tasks comparisons (45%) showed significant impairment. While the benzodiazepines with longer half-lives tended to show more overall daytime impairment, the pattern and magnitude of the deficits did not follow the length of their half-lives.

In the recent 37-night study of flurazepam (30 mg), triazolam (0.5 mg), and placebo cited earlier, there were no statistically significant differences between the three groups in daytime performance. The three groups also did not differ statistically on drowsiness as measured by the Multiple Sleep Latency Test (Mitler et al. 1984). However, when the pattern of change from baseline for each group was examined, it was clear that the next-day performance of patients receiving flurazepam was most affected (Johnson et al. 1984).

In summary, with chronic use, dose level of a sedative-hypnotic is the best predictor of the presence or absence of a next-day performance decrement. In acute use and at comparable dose levels, hypnotics with shorter half-lives are less likely to produce daytime impairment. With continued use, build-up of plasma levels of the hypnotic or its metabolite is not correlated with performance decrement. In many instances, tolerance may be seen.

Effect During Withdrawal

With the increase in availability and use of hypnotics with intermediate and short half-lives, a potential clinical problem has been identified--namely, "rebound insomnia" - withdrawal from hypnotics with short half-life, though not from those with a long half-life, immediately impairs the quality of sleep (Kales et al. 1979). Similarly, Oswald et al. (1982) found that sleep was poorer during the first three nights after discontinuation of lormetazepam (2 mg) (half-life 10-12 hours) after 32 weeks of administration. They, however, reported that patients in the same study who had received nitrazepam (5 mg) (half-life 24-30 hours) also experienced poorer sleep upon discontinuation, but this consisted of poor sleep on one or more nights over a two-week period.

To examine whether there was a withdrawal problem after 37 nights of use, the triazolam, flurazepam, and placebo data from the Stanford study were reanalyzed by Johnson et al. (1984). The patients receiving triazolam experienced a significant increase in sleep latency on the first two nights after withdrawal, but this had returned to baseline values by the third night (Fig. 5). Awake time after sleep onset and before final awakening, as well as awake time after final awakening, during withdrawal showed no significant changes from pretreatment values. However, 3

of the patients had poorer sleep, sleep efficiency of less than 70 percent, on one night after the initial two withdrawal nights.

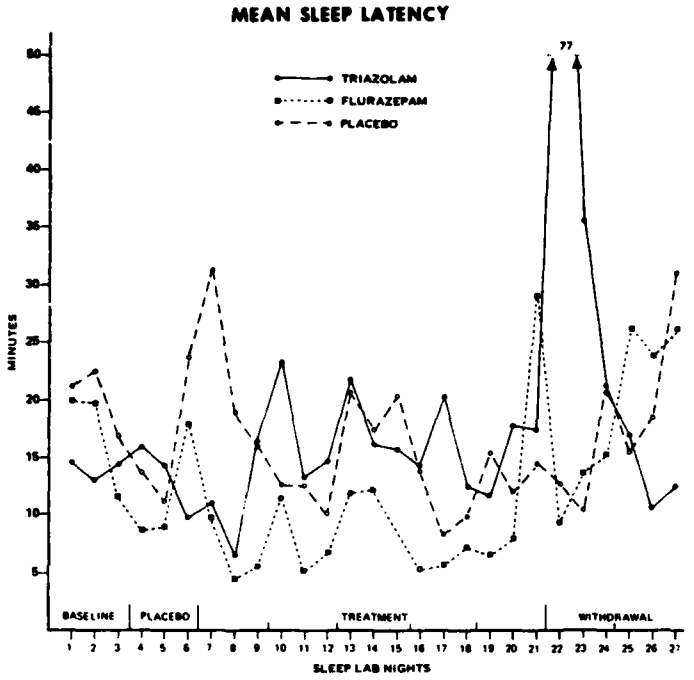

Fig. 5. Mean EEG sleep latency in minutes on sleep laboratory nights during baseline (B), placebo (P), treatment (T), and withdrawal (W) (from Johnson et at. 1984).

During withdrawal, the sleep latency and awake time after the onset of sleep in the 7 patients who had received flurazepam were not significantly different from the values of the placebo group or from their own pretreatment values. Five of these patients, however, experienced poorer sleep, sleep efficiency below 70 percent, during withdrawal than before treatment. The cause of this poor sleep is unknown, but poor sleep was related neither to the plasma level of N-desalkylflurazepam nor to the rate of decrease of the plasma level during withdrawal. Sleep was poorer for only one or two nights and, in contrast to the experience of the patients who had taken triazolam, the poor sleep occurred on different nights for different patients throughout the two-week interval. No patient taking flurazepam experienced poor sleep on the first night after withdrawal and, if they did at any time, it tended to be later than the fourth night after withdrawal. The cause of the poor sleep in some patients was an increase in sleep latency, and in others it was an increase in awake time after the onset of sleep.

Withdrawal sleep for the placebo patients was similar to that during the treatment period. Only one patient had a sleep efficiency below 80 percent on any night and only one patient had a poorer night of sleep during withdrawal than was present during baseline.

In summary, after chronic use, patients should be advised that sleep on one or two nights during withdrawal may be poor. For drugs with a short elimination half-life, sleep tends to be poor on nights early in the withdrawal period, but, for hypnotics

with a long elimination half-life, such effects are on average much less marked and may occur at any time during the ensuing two weeks.

CONCLUSIONS

For clinical purposes, our results and the findings of others support the recommendation of the National Institutes of Health, Consensus Panel on Drugs and Insomnia (1983), i.e., use the lowest dose for the shortest period of time. The impact of half-life on efficacy and next-day performance, however, is more complex. Other pharmacokinetic properties must be considered, e.g., volume of distribution (Greenblatt et al. 1983). Measurement of the relative affinity of each of the sedative-hypnotics for the benzodiazepine receptor is now feasible and provides the opportunity for gleaning new information on the action of benzodiazepines in the CNS (Sieghart 1983). Ellinwood et al. (1984), using a pharmacokinetic pharmacodynamic receptor binding model, found that the relative receptor occupancy of diazepam was more significantly related to performance than was the unbound plasma drug level.

The marked individual differences in response to similar plasma drug levels plus the tendency for tolerance or adaptation to occur to both efficacy and hangover effects limit the probability that significant correlations between plasma benzodiazepine levels and behavioral measures will be found during chronic use. Clearly, the role and importance of N-desalkylflurazepam are yet to be determined. Further, the relationship of plasma levels to presence in the brain and to action at specific receptor sites is not clearly understood. Though its neurophysiological and behavioral significances are still unknown, the sensitivity of sleep spindles to the use of benzodiazepine sedative-hypnotics suggests that more attention should be given to this EEG change as a marker of the presence of benzodiazepine in the brain.

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Recently, research emphasis has shifted from assessment of efficacy of benzodiazepine hypnotics to investigation of pharmacokinetics and pharmacodynamics. In this paper, we review our work and draw upon the published literature to examine the effects of benzodiazepine hypnotics on the structure of sleep, arousal threshold during sleep, and the impact of bedtime hypnotic use on next-day performance. We also describe the effects of discontinuation of use of long- and short-acting sedative-hypnotics.

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Our results indicate that the half-life of benzodiazepine hypnotics is not the best predictor of next-day performance effects, arousal threshold effects, or the nature of EEG changes during sleep. Other pharmacokinetic properties, such as volume of distribution, must also be considered. Long and short half-life benzodiazepines both may produce a "rebound insomnia", although the time of occurrence seems to differ. The marked individual differences in response to similar drug plasma levels plus processes of tolerance and adaptation limit the probability that significant correlations between plasma levels and behavioral levels will be found over individuals during chronic use. As dose level is the best predictor of next-day effects, the smallest effective dose should be prescribed.

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